

EDITORIAL COMMENT

The Points for Pacing*

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In this issue of the *Journal*, the study by Higgins et al. (1) from the trial of resynchronization therapy provides the opportunity to assess the current status of both the application of biventricular pacing and the construction of trial end points for new therapies in heart failure (HF). The devices used in this trial clearly improved functional capacity in those patients with major functional limitation at baseline, a finding that reinforces the functional benefit seen with similar devices and populations in other trials. The strength and relevance of this emerging evidence stand despite the interposition of an end point that did not show benefit in this trial.

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FUNCTIONAL BENEFIT FOR ADVANCED HF

Therapies proven beneficial for HF have done so largely by showing decreases in disease progression and mortality (2–5). The third target of therapy is the limiting symptoms of HF. It is this third target that has been hit squarely by biventricular pacing in appropriate candidates.

Of 581 patients originally identified in the trial, 490 patients were randomized as planned 30 days after the procedure. Of the 91 patients not randomized, 14 withdrew before the procedure and 1 withdrew after the procedure, 66 did not have successful coronary sinus lead insertion, and 10 died (2 of defibrillator testing complications, 5 of HF, 2 of other cardiac causes, and 1 of unspecified reasons). It is a strength of this trial that optimization of medical therapy took place after the procedure for 30 days, during which 40% of New York Heart Association (NYHA) functional class III to IV patients improved to class I to II whereas 19% of class II patients worsened, changes that might otherwise have clouded the effect of the intervention. Nonetheless, the trial population for analysis might be considered to be the original 581 patients, as was done for the meta-analysis of biventricular pacing trials (6), rather than the 480 patients (84%) randomized at 30 days after device implantation. The current trial is an amalgam of both transthoracic (11%) and transvenous devices (89%) and three-month and six-month follow-up. The original end point was peak oxygen consumption, a rigorous measurement of functional capacity. Multiple factors apparently influenced the decision to

change the end point to a composite of mortality, HF hospitalizations, and ventricular tachyarrhythmias requiring therapy.

Functional capacity improved significantly in the overall patient cohort, as indicated by an average increase of 1 ml/kg/min versus no change in peak oxygen consumption and an increased 6-min walk distance of 35 versus 17 m. These changes were driven by changes in the patients with NYHA functional class III to IV because only minor improvements could occur in the patients who had few symptoms at baseline. Improvements in the quality of life questionnaire and NYHA functional class were also seen in the patients with class III to IV symptoms at baseline. These more subjective changes lend support to the overall picture of clinical improvement, but it is harder to interpret if patients and physicians recognized the active therapy.

There is now a robust body of evidence supporting the functional benefit in patients with major symptoms of HF. The data from this experience are comparable to those from the Pacing Therapies for Congestive Heart Failure (PATH-CHF), MUSTIC, MIRACLE, and MIRACLE-ICD trials (7–10). The limitation of symptomatic benefit to those with NYHA functional class III or worse symptoms also is consistent with previous experience (Fig. 1). In the MIRACLE-ICD trial of a similar population requiring ICD therapy, patients who were NYHA functional class II had good functional capacity at baseline with little evidence for any increase (9).

The post-approval experience with biventricular pacing has provided reassurance that the enthusiasm of investigators and patients perceiving dramatic clinical improvement during the original trials has been warranted. At the extreme end, patients undergoing biventricular pacing are frequently leaving the waiting list for cardiac transplantation (11). The magnitude of early benefit for functional capacity in the trials and in office settings far exceeds that described for the initiation of angiotensin-converting enzyme inhibitors or beta-adrenergic receptor antagonists (3,12). While decreasing disease progression and prolonging survival, the pharmacologic therapies may prevent worsening of functional capacity more effectively than they have improved it once it has declined, with the exception of diuretics for symptomatic fluid overload. In fact, the inability of quality of life measures to reliably identify clinical improvement on medications led to some question of whether the tools were sufficiently sensitive. The recent trials of biventricular pacing have validated the functional benefit of this therapy but have also validated our ability to identify major symptomatic improvement when it occurs in this HF population.

SURVIVAL AND DISEASE PROGRESSION

Measurable improvement in functional capacity and quality of life represents an intrinsically worthwhile target for therapy in patients with limiting symptoms of HF. Although disease progression and survival do not need to be

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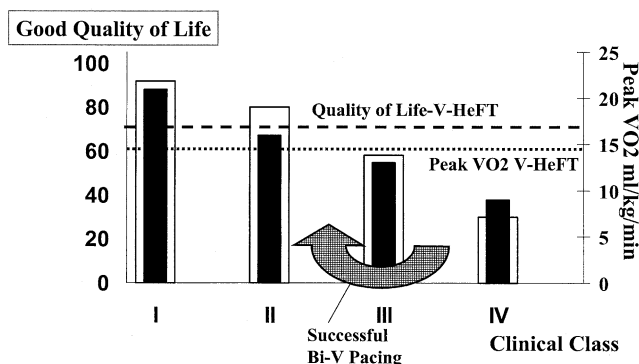


Figure 1. Estimated impact of successful biventricular (Bi-V) pacing in patients typical of those in the major trials. Good quality of life is calculated as 105 minus the Minnesota Living with Heart Failure Questionnaire score (therefore, a higher score is better on this graph), shown in **open bars**. **Solid bars** are peak oxygen consumption (VO₂) during exercise testing. For comparison, average values at baseline are superimposed on the population with mild-to-moderate heart failure in the Vasodilator Heart Failure Trials (V-HeFT) (3).

improved for this therapy to be viable, any worsening of these end points would be of concern. Current data indicate no worsening of the more solid end points of hospitalizations and mortality. It has been suggested that biventricular pacing may increase the risk of torsade de pointes (13), but the current trial and others have found no evidence of increased clinical tachyarrhythmias.

There is in fact a strong trend shown here for decreased hospitalizations, as one would expect from a therapy that improves symptoms without major adverse effects. Because the severity of HF and prognosis are mirrored in the frequency of hospitalization, we might then expect that robust symptomatic improvement could be associated with better survival. The meta-analysis of biventricular pacing trials (14) showed a 51% decrease in HF mortality as described by Bradley et al. (6). Preliminary data from the recently concluded COMPANION trial indicates a decrease in total mortality as well. It should be emphasized, however, that such an improvement in survival might not be required of a therapy that can stimulate sustained improvement in functional capacity when stacked onto the multiple therapies already recommended for survival.

Resynchronization is associated acutely with improved contractility measured as dP/dt, decreased mitral regurgitation, and lower left ventricular filling pressures (14,15). Maintenance of these improvements might be expected to lead to chronic remodeling, which was seen for NYHA functional class II as well as class III/IV HF in this experience and has been observed previously to a modest degree with both left ventricular size and ejection fraction (16). The consistent improvement in systolic blood pressure additionally allows up-titration of the medications with potential remodeling benefits. Caution is appropriate, however, when interpreting parameters of remodeling in this setting. The pacing itself may cause immediate functional changes that will partially revert as soon as pacing is halted. Perhaps more important, surrogate end points that do not

carry intrinsic value for survival or function can be altered in ways that bypass the desired effect, particularly with a novel type of therapy. The surgical left ventriculectomy procedure as put forth by Batista decreased both left ventricular size and ejection fraction but most patients went on to cardiac replacement therapies or died (17). It is reassuring that biventricular pacing does not worsen parameters of disease progression. However, disease progression does not have to be improved to justify biventricular pacing to improve symptoms that limit daily life. If consideration of biventricular pacing extends to patients without limiting symptoms, such as in the NYHA functional class II patients with ICD indications in this trial, the benefit to decrease disease progression would have to be robust and confirmed with clinical end points over a longer trial period.

WHO BENEFITS FROM RESYNCHRONIZATION?

Ambulatory patients with severe symptoms on standard oral medications seem most likely to derive benefit. Within that population, the trials have focused on patients with QRS width over 130 ms, although most trial subjects have had QRS duration over 160 ms. The QRS duration does not reliably predict the degree of dyssynchrony seen on echocardiogram or the magnitude of clinical improvement (18). Our current knowledge remains very limited in terms of the most appropriate subjects, the optimal lead positions, and the adjustment of atrioventricular, interventricular, and intraventricular synchrony.

Biventricular pacing as currently provided does not impact on the majority of patients with advanced HF. When calculating the potential target population, it should be borne in mind that only one-half of HF occurs with reduced left ventricular ejection fraction. Among patients with persistent functional limitation and low left ventricular ejection fraction, the proportion with a favorable pattern of dyssynchrony as currently determined by QRS duration and morphology is in the range of 30%. Positioning in the coronary sinus is possible in 85% to 95% of cases. Occasional deaths result from coronary sinus injury or from testing of the defibrillator function of combined devices. After successful implantation, perhaps 5% to 15% of patients have problems with diaphragmatic pacing or lead instability that prevent continued pacing. Of those receiving pacing, improvement is seen in approximately 60% to 70%. At present, biventricular pacing is thus predicted to improve clinical status for 15% to 20% of patients with advanced HF and reduced left ventricular ejection fraction. Extension to patients with atrial fibrillation (19) or to chronic right ventricular pacemaker dependence is under investigation.

FROM THE BEGINNING TO END POINTS

The major end points of therapy for HF are survival, functional capacity, and disease progression. Embarking upon a trial involves selection of an end point that is measurable and interpretable, sensitive to the therapy being tested, and clinically relevant, as summarized by Fleming

and DeMets (20). Choosing the “right” end point for a trial often involves compromise between the best information needed to justify use of a therapy and the best chance of having a “positive” trial.

The construction of end points for HF can be seen as an emerging craft. It has evolved from a single component in early trials to the complex composite. The dual composite is appropriate for key end points other than mortality, such as hospitalization, to allow for competing outcomes. The patient who is dead cannot be hospitalized but must be counted as a bad outcome. Other composites have become, however, increasingly complex. In the current trial, death and hospitalization were combined with ventricular tachyarrhythmias. This component may have been added to balance efficacy with risk; torsade de pointes has been suggested to be triggered by the inhomogeneity of biventricular pacing (13). Alternatively, at the time the study was designed, there was some optimism that ventricular arrhythmias would be decreased by biventricular pacing. Composites can become even more complex to combine feel-good scales with mortality and other adverse events. In some trials, composites may be designed for statistical success that then allows consideration of more vital secondary end points.

In this trial, the end point chosen was highly relevant but not sensitive to the treatment effect. Is the evidence for functional benefit weakened in this trial because the primary end point was not met? The power to exclude chance is not the same as truth. There is generally a truth that ultimately emerges, even if sometimes delayed or ignored. Biventricular pacing does improve functional capacity for many patients, whether functional capacity is the primary end point, the 19th, or absent from the list. The choice and success of the end point have profound importance for the initial sponsors. The truth, however, remains impervious to the prediction or parsimony of its seekers.

The trial of biventricular pacing reported by Higgins et al. (1) re-enforces the rapid acceptance of this new technology as treatment for the symptoms in advanced heart failure. Support is building for the hypothesis that resynchronization may also influence disease progression, as measured by the surrogates established for pharmacologic therapy. To extend this procedure to prevent HF progression earlier in the course of disease would require further trials, with careful consideration of new end points specific to pacing therapies.

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